PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classificati n 6 : A61K 9/20, 31/40, 31/215, 31/19, 31/135 — A1

(11) International Publicati n Number: WO 96/18386

(43) International Publication Date: 20 June 1996 (20.06.96)

(21) International Application Number: PCT/IE95/00062

(22) International Filing Date: 14 December 1995 (14.12.95)

(30) Priority Data:

940969	14 December 1994 (14.12.94)	IE
940971	14 December 1994 (14.12.94)	IE
950583	31 July 1995 (31.07.95)	IE
950584	31 July 1995 (31.07.95)	IE
950586	31 July 1995 (31.07.95)	IE

(71) Applicants *(for all designated States except US)*: ENBALT TRADING LIMITED [IE/IE]; Setanta Centre, 4th floor, Nassau Street, Dublin 2 (IE). BIOGLAN IRELAND (R & D) LIMITED [IE/IE]; 1 Stokes Place, Saint Stephens Green, Dublin 2 (IE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: McCARTHY, Paul [IE/IE]; Ballyvaughan, Clonmel, County Tipperary (IE). DONEGAN, Ann [IE/IE]; 8 Cloughcarigeen, Kilsheelan, County Tipperary (IE). PATTISON, John [IE/IE]; 52 Hazelwood, Shankill, County Dublin (IE). O'SULLIVAN, Richard [IE/IE]; 15 Melitta Park, Kildare, County Kildare (IE).

(74) Agents: O'CONNOR, Donal, H. et al.; Cruickshank & Co., 1 Holles Street, Dublin 2 (IE).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DE (Utility model), DK, DK (Utility model), EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL TABLET FORMULATIONS FOR DIRECT COMPRESSION

(57) Abstract

Tablets are produced by directly compressing a mixture formed by dry blending an active pharmaceutical ingredient, direct compression lactose, a lubricant such as magnesium stearate and an inhibitor, especially maize starch. The active pharmaceutical ingredient includes xybutynin, bumetanide, indapamide and particularly selegiline. The inhibitor prevents interaction between the direct compression lactose and the active pharmaceutical ingredient.

FOR THE PURPOSES OF INFORMATION ONLY

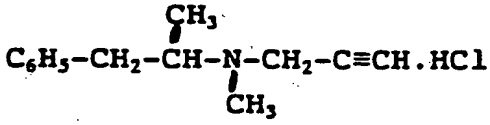
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

Pharmaceutical tablet formulations for direct compression

The invention relates to a pharmaceutical tablet formulation of an active pharmaceutical ingredient and to a method for producing such tablets.

UK-A-1,153,578 describes selegiline hydrochloride which is the compound of the formula



It has monoamine oxidase inhibitor activity and is used in the treatment of Parkinsons disease and as a coronary dilator, hallucinogenic and anti-depressive agent and also as a tranquilliser, analgesic and an appetite suppressant.

It is known to formulate selegiline in tablet form using conventional wet granulation techniques. However, to date it has not been possible to produce a satisfactory tablet composition of selegiline by direct compression techniques. Similar problems have arisen with other active pharmaceutical ingredients.

Direct compression is the preferred technique since it is considered that fewer chemical stability problems are associated with this technique in comparison with the wet granulation process as moisture is considered to be a primary cause of instability in tablet dosage forms. In addition to the advantage of improved active ingredient stability, the use of direct compression makes it unnecessary to use applied heat to dry the damp granul . Other benefits associated with direct compression are related to particle size uniformity.

This invention therefore is directed towards a direct compression pharmaceutical tablet formulation of an active pharmaceutical ingredient.

According to the invention, there is provided a direct compression pharmaceutical tablet formulation comprising:

an active pharmaceutical ingredient,

a direct compression excipient which interacts with the active pharmaceutical ingredient, and

an amount of an inhibitor to reduce the interaction between the direct compression excipient and the active pharmaceutical ingredient.

In a preferred embodiment of the invention the formulation contains an amount of the inhibitor to substantially prevent the interaction between the direct compression excipient and the active pharmaceutical ingredient.

In one preferred embodiment of the invention the weight ratio of inhibitor to the active pharmaceutical ingredient is from 1:50 to 4:1, ideally from 8:5 to 12:5. Preferably the inhibitor includes a starch, starch-derived or cellulose-derived product, especially maize starch.

In another embodiment of the invention, the inhibitor includes a crospovidone based product.

In a preferred embodiment of the invention the excipient is direct compression lactose and/or micr crystalline cellulose.

The weight ratio of direct compression lactose to active pharmaceutical ingredient is preferably from 2:1 to 100:1 most preferably from 7:1 to 50:1, ideally from 8:1 to 11:1.

The weight ratio of microcrystalline cellulose to active pharmaceutical ingredient is preferably from 2:1 to 100:1, most preferably from 3:1 to 17:1, ideally from 4:1 to 16:1.

In one embodiment of the invention, the formulation includes a lubricant, preferably from 0.1% to 5%, most preferably approximately 0.25% by weight of the formulation. The lubricant may be magnesium stearate, zinc stearate, calcium stearate, stearic acid or combinations of these materials.

In one embodiment of the invention, the formulation includes an antioxidant or other suitable stabiliser to enhance the stability of the tablet formulation. Preferably the antioxidant is present in an amount of from 0.5% to 2% by weight of the formulation.

In another embodiment of the invention the formulation may include glidants, disintegrants, fillers, wetting agents, stabilisers, binders, or combinations of these materials.

The active pharmaceutical ingredient may be selegiline or a pharmaceutically acceptable salt thereof, preferably selegiline hydrochloride. The active pharmaceutical ingredient may also be th r compounds including oxybutynin or a pharmaceutically acceptable salt thereof, preferably oxybutynin chl rid ; bumetanide or a pharmaceutically acceptable salt thereof; or indapamide or a pharmaceutically acceptable salt th reof, preferably indapamid hemihydrate.

The invention also provides a method of preparing a tablet by preparing a formulation according to the inventi n and directly compressing said formulation to form a tablet.

The invention further provides a method for producing tablets of an active pharmaceutical ingredient comprising the steps of:-

mixing the active pharmaceutical ingredient, a lubricant, a direct compression excipient, and an amount of an inhibitor to substantially prev nt interaction between the direct compression lactose and the active pharmaceutical ingredient; and

directly compressing the mixture thus formed to form tablets.

Preferably the formulation includes a lubricant and the method includes the step of mixing the ingredients except the lubricant and subsequently adding the lubricant. Preferably the mixing is a dry blending technique. The excipient is preferably direct compression lactose.

The inhibitor preferably includes a starch, starch-derived or cellulose-derived product. Alternatively, th inhibitor includes a crospovidone based product.

The invention will be more clearly understood from the following description thereof given by way of example only.

In each cas , the formulation is a direct compression formulation. Th ingr dients wer weighed ut and all the ingredients except the lubricant were added to a receptacle and dry blended for about 6 minutes. Th

lubricant (in these cases magnesium stearate) was then added and the mixture is blended for a further 2 minutes. Tablets were then formed from the blend by conventional direct compression techniques.

In Examples A and 1 to 4, selegiline hydrochloride was used as the active ingredient. However, it will be appreciated that selegiline base or any pharmaceutically acceptable salt thereof may be used as the activ ingredient. Similar comments apply to the examples referring to other active ingredients. In examples B and 5 oxybutynin chloride was used. In example 9 indapamide hemihydrate was used.

All of the excipients used in the examples are of pharmaceutical grade.

Magnesium Stearate:	consists mainly of magnesium stearate with variabl proportions of magnesium palmitate and/or magnesium oleate. It is a tablet lubricant.
Zinc Stearate:	consists mainly of zinc stearate with variable proportions of zinc palmitate and zinc oleate. It is a tablet lubricant.
Sodium Lauryl Sulfate:	an anionic surfactant us d as a detergent and wetting agent in tablet formulati ns.

Croscarmellose Sodium: is a cross-linked polymer of carboxymethylcellulose sodium. It is a tablet disintegrant.

Sodium Starch Glycolate: is the sodium salt of a poly-α-glucopyranose in which some of the hydroxyl groups are in the form of carboxymethyl ether. It is a tablet disintegrant.

Crospovidone: is a water insoluble synthetic cross-linked homopolymer of N-vinyl-2-pyrollidone. It is a tablet disintegrant.

Microcrystalline Cellulose: is a purified, partially depolymerised cellulose and is used as a diluent and has som lubricant and disint grant properties.

Direct Compression Lactose (DC Lactose): is direct compression grade of lactose which is more fluid and more compressible than crystalline or powdered lactose.

Various proprietary brands of direct compression lactose are commercially available. In the examples given below, th brand of dir ct compression lact se used was Tablettose 80 available from Meggle GmbH of Germany. We have also achieved similar results using Pharmatose DC11 which is available from DMV International of The Netherlands.

It will be appreciated that various similar formulations to those described below may be prepared by scaling up or down the components of the mixture so that the new formulation is quantitatively proportional to those given below. For example, formulations containing 10 mgs of selegiline may be prepared in this way. Similarly, an oxybutynin formulation may be prepared in this way with 2.5 mg rather than 5 mg of active. In addition, a bumetanide formulation may also be prepared in this way with 1 mg rather than 5 mg of active ingredient.

EXAMPLE A

A batch of tablets were prepared by direct compression. Each tablet had the following composition:-

5 mg	selegiline hydrochloride
85 mg	DC Lactose

The tablets gave an assay of 91.8%.

This example illustrates the low assay that results when tablets of selegiline are manufactured by direct compression techniques using direct compression lactose.

EXAMPLE 1

A batch of tablets were prepared by direct compression. Each tablet had the following composition:-

5 mg	selegiline hydrochloride
52.75 mg	DC Lactose
24 mg	microcrystalline cellulose
8 mg	maize starch
0.25 mg	magnesium stearate

The tablets gave an assay of 99.5%.

It will be noted that the use of an inhibitor, in this case maize starch, radically improves the assay result.

EXAMPLE 2

A batch of tablets were prepared by direct compression. Each tablet had the following composition:-

5 mg	selegiline hydrochloride
48.75 mg	DC Lactose
24 mg	microcrystalline cellulose
12 mg	maize starch
0.25 mg	magnesium stearate

The tablets gave an assay of 97.94%.

Using a larger amount of maize starch and less DC Lactose did not significantly effect the assay.

EXAMPLE 3

A batch of tablets were prepared by direct compression. Each tablet had the following composition:-

5 mg	selegiline hydrochloride
48.75 mg	DC Lactose
24 mg	microcrystalline cellulose
11 mg	maize starch
1 mg	citric acid
0.25 mg	magnesium stearate

The tablets gave an assay of 99.6%.

Th addition of an antioxidant, in this case citric acid, is to counteract any oxidation reactions in storage.

EXAMPLE 4

A batch of tablets were prepared by direct compressi n. Each tablet had the following composition:-

5 mg	selegiline hydrochloride
49.45 mg	Direct Compression Lactose
24 mg	Microcrystalline Cellulose
11 mg	Maize Starch
0.55 mg	Zinc Stearate

The tablets gave an assay of 100.7%

From extensive research and development in producing tablets of selegiline by direct compression techniques, we have noticed a very significant interaction between selegiline hydrochloride and conventional bulking agents such as DC Lactose and microcrystalline cellulose. It has not been possible using conventional formulations to produce a tablet of selegiline by direct compression without a very significant adverse affect on the assay results for the tablets produced. In all cases, the assay was found to be less than 95%, in some cases, as low as 70%. It is not fully understood why such poor assay results were obtained. It is, however, speculated that there may be an interaction between the selegiline and the DC Lactose and microcrystalline cellulose, resulting possibly in the formation of a complex which adversely affects the amount of selegiline detectable or availabl on assay. We have surprisingly found that the interaction is avoided and good assay r sults are obtain d if an inhibitor, particularly maiz starch, is incorporated especially in th amounts mentioned above.

It will be appreciated that it may be possible to use direct compression excipients either in addition to or as

an alternative either to direct compression lactose or microcrystalline cellulose. Such direct compression excipients include calcium hydrogen phosphate, compressible sugar, dextrates, and pregelatinized starch.

It will be appreciated that the formulation may include any suitable lubricant such as magnesium stearate or zinc stearate as described above or other stearic acid salts such as calcium stearate. Other suitable lubricants may also be incorporated, including glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type 1, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulphate, sodium stearyl fumarate, stearic acid and talc.

It will also be appreciated that while the presence of an antioxidant may not be essential, in cases where such an antioxidant is used it may be selected from one or more of the following: alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, citric acid, fumaric acid, malic acid, propylgallate, sodium ascorbate, sodium metabisulphite.

We have also found that the interactions described above also apply to other active pharmaceutical ingredients. The following examples illustrate how similar techniques may also be applied to direct compression pharmaceutical tablet formulations of active ingredients other than selegiline.

EXAMPLE B - COMPARISON

A batch of tablets were prepared by direct compression. Each tablet had the following composition:-

5 mg	oxybutynin chloride
174 mg	DC Lactose
1 mg	Magnesium Stearate

The tablets gave an assay of 88.3%.

EXAMPLE 5

A batch of tablets were prepared by direct compression. Each tablet had the following composition:-

5 mg	oxybutynin chloride
119 mg	DC Lactose
43 mg	microcrystalline cellulose
12 mg	crospovidone
1 mg	magnesium stearate

The tablets gave an assay of 97.9%.

EXAMPLE C - COMPARISON

A batch of tablets were prepared by direct compression. Each tablet had the following composition.

5	mg	bumetanide
343	mg	DC Lactose
2	mg	magnesium Stearate

The tablets gave an assay of 91%.

EXAMPLE D - COMPARISON

A batch of tablets were prepared by direct compression. Each tablet had the following composition.

5	mg	bumetanide
343	mg	microcrystaline cellulose
2	mg	magnesium stearate

The tablets gave a assay of 93.7%.

EXAMPLE 6

A batch of tablets were prepared by direct compression. Each tablet had the following composition.

5	mg	bumetanide
237.5	mg	DC Lactose
80	mg	microcrystalline cellulose
25	mg	crospovidone
2.5	mg	magnesium stearate

The tablets gave an assay of 97.4%.

EXAMPLE 7

A batch of tablets were prepared by direct compressi n. Each tablet had the following composition.

5 mg	bumetanide
237.5 mg	DC Lactose
80 mg	microcrystalline cellulose
25 mg	maize starch
2.5 mg	magnesium stearate

The tablets gave an assay of 98.2%.

EXAMPLE 8

A batch of tablets were prepared by direct compression. Each tablet had the following composition.

5 mg	bumetanide
241 mg	DC Lactose
80 mg	microcrystalline cellulose
17 mg	croscarmellose sodium
5 mg	sodium lauryl sulphate
2 mg	magnesium stearate

The tablets gave an assay of 97.9%

EXAMPLE 9

A batch of tablets were prepared by direct compression. Each tablet had the following c mposition:-

2.5 mg	indapamid hemihydrate
82.75 mg	DC Lactose
4 mg	carboxymethyl starch
0.75 mg	magnesium stearate.

The tablets gave an assay of 100.4%.

It will be appreciated that similar techniques may be applied to produce direct compression tablet formulations of other active pharmaceutical ingredients which interact with direct compression excipients.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

CLAIMS

1. A direct compression pharmaceutical tablet formulation comprising:

an active pharmaceutical ingredient,

a direct compression excipient which interacts with the active pharmaceutical ingredient,

and an amount of an inhibitor to reduce the interaction between the direct compression excipient and the active pharmaceutical ingredient.

2. A direct compression pharmaceutical tablet formulation as claimed in claim 1 wherein the formulation contains an amount of the inhibitor to substantially prevent the interaction between the direct compression excipient and the active pharmaceutical ingredient.

3. A formulation as claimed in claim 1 or 2 wherein the weight ratio of inhibitor to the active pharmaceutical ingredient is from 1:50 to 4:1.

4. A formulation as claimed in any of claims 1 to 3 wherein the weight ratio of inhibitor to the active pharmaceutical ingredient is from 8:5 to 12:5.

5. A formulation as claimed in any preceding claim wherein the inhibitor includes a starch, starch-derived or c llulose-derived product.

6. A formulation as claimed in any pr ceding claim wherein the inhibitor includes a maize starch.

7. A formulation as claimed in any proceeding claim in which the inhibitor includes a crospovidone based product.

8. A formulation as claimed in any preceding claim wherein the excipient includes direct compression lactose.

9. A formulation as claimed in claim 8 wherein the weight ratio of direct compression lactose to th active pharmaceutical ingredient is from 2:1 to 100:1.

10. A formulation as claimed in claim 8 or 9 wherein the weight ratio of direct compression lactose to the active pharmaceutical ingredient is from 7:1 to 50:1.

11. A formulation as claimed in any of claims 8 to 10 wherein the weight ratio of direct compression lactose to the active pharmaceutical ingredient is from 8:1 to 11:1.

12. A formulation as claimed in any preceding claim wherein the excipient includes microcrystalline cellulose.

13. A formulation as claimed in claim 12 wherein the weight ratio of microcrystalline cellulose to active pharmaceutical ingredient is from 2:1 to 100:1.

14. A formulation as claimed in claim 12 or 13 wherein the weight ratio of microcrystalline c llulose to active pharmaceutical ingredient is from 3:1 to 17:1.

15. A formulation as claimed in any of claims 12 to 14 wherein the weight ratio of microcrystalline cellulose to active pharmaceutical ingredient is from 4:1 to 16:1.

16. A formulation as claimed in any preceding claim including a lubricant.

17. A formulation as claimed in claim 16 wherein the lubricant is present in an amount from 0.1% to 5% by weight of the formulation.

18. A formulation as claimed in claim 17 wherein the lubricant is present in an amount of approximately 0.25% by weight of the formulation.

19. A formulation as claimed in any preceding claim including an antioxidant or other suitable stabiliser to enhance the stability of the tablet formulation.

20. A formulation as claimed in claim 19 wherein the antioxidant is present in an amount from 0.5% to 2% by weight of the formulation.

21. A formulation as claimed in any proceeding claim including either a glidant, a disintegrant, a filler, a wetting agent, stabiliser, a binder or any combination of these materials.

22. A formulation as claimed in any preceding claim wher in the active pharmaceutical ingredient is selegilin or a pharmac utically acceptable salt thereof, pr ferably sel giline hydrochloride.

23. A formulation as claimed in any of claims 1 to 21 wherein the active pharmaceutical ingredient is

oxybutynin or a pharmaceutically acceptable salt thereof, preferably oxybutynin chloride.

24. A formulation as claimed in any of claims 1 to 21 wherein the active pharmaceutical ingredient is bumetanide or a pharmaceutically acceptable salt thereof.

25. A formulation as claimed in any of claims 1 to 21 wherein the active pharmaceutical ingredient is indapamide or a pharmaceutically acceptable salt thereof, preferably indapamide hemihydrate.

26. A direct compression pharmaceutical tablet formulation substantially as hereinbefore described with reference to examples 1 to 3.

27. A direct compression pharmaceutical tablet formulation substantially as hereinbefore described with reference to example 4.

28. A direct compression pharmaceutical tablet formulation substantially as hereinbefore described with reference to example 5.

29. A direct compression pharmaceutical tablet formulation substantially as hereinbefore described with reference to examples 6, 7 and 8.

30. A direct compression pharmaceutical tablet formulation substantially as her inbefore describ d with ref r nce to xample 9.

31. A method of preparing a tablet comprising:

preparing a formulation as claimed in any preceding claim; and

directly compressing said formulation into a tablet.

32. A method for producing tablets of an active pharmaceutical ingredient comprising the steps f:-

mixing the active pharmaceutical ingredient, a lubricant, a direct compression excipient, and an amount of an inhibitor to reduce interaction between the direct compression excipient and the active pharmaceutical ingredient; and

directly compressing the mixture thus formed to form tablets.

33. A method as claimed in claim 32 wherein the method includes the step of mixing the ingredients except the lubricant; subsequently adding the lubricant; and further mixing the ingredients.

34. A method as claimed in claim 32 or 33 wherein the mixing is performed using a dry blending technique.

35. A method as claimed in any of claims 32 to 34 wherein the direct compression excipient includes direct compression lactose.

36. A method as claim d in any of claims 32 to 35 wherein the inhibitor includes a starch, a starch-derived product, a cellulose-derived pr duct or a d rivative th re f.

37. A method as claimed in any of claims 32 to 36 wherein the inhibitor includes a crospovidone based product.

38. A method as claimed in any of claims 31 to 37 wherein the active pharmaceutical ingredient is selegiline or a pharmaceutically acceptable salt thereof, preferably selegiline hydrochloride.

39. A method for producing tablets of an activ pharmaceutical ingredient substantially as hereinbefore described with reference to examples 1 to 9.

40. A method for producing tablets of selegiline substantially as hereinbefore described with reference to examples 1 to 4.

41. A method for producing tablets of oxybutynin substantially as hereinbefore described with reference to example 5.

42. A method for producing tablets of bumetanide substantially as hereinbefore described with reference to examples 6, 7 and 8.

43. A method for producing tablets of indapamide substantially as hereinbefore described with reference to example 9.

44. Tablets of an active pharmaceutical ingredient when ver produced by a method as claimed in any of claims 31 to 43.

45. Tablets of selegiline or a pharmaceutically acceptable salt thereof, pref rably sel giline

hydrochloride whenever produced by a method as claimed in any of claims 31 to 40.

46. Tablets of oxybutynin or a pharmaceutically acceptable salt thereof, preferably oxybutynin chloride whenever produced by a method as claimed in any of claims 31 to 39 or 41.

47. Tablets of bumetanide or a pharmaceutically acceptable salt thereof whenever produced by a method as claimed in any of claims 31 to 39 or 42.

48. Tablets of indapamide or a pharmaceutically acceptable salt thereof, preferably indapamide hemihydrate whenever produced by a method as claimed in any of claims 31 to 39 or 43.

49. A tablet prepared or preparable from a formulation as claimed in any of claims 1 to 30.

INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/IE 95/00062

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K31/40 A61K31/215 A61K31/19 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 08463 (RHONE POULENC RORER SA) 29 May 1992	1-3,5, 12,16, 17,31, 32,34, 36,44,49
Y	see page 7; example 2 see above	4,6-11, 13-15, 18-30, 33,35, 37-43, 45-48

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 March 1996	07. 05. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Herrera, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. .onal Application No
PCT/IE 95/00062

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 511 767 (MERCK & CO INC) 4 November 1992 see page 2, line 27 - line 29 see page 5 - page 6; examples 1-12	1-3,5,8, 12,16, 17, 31-36, 44,49
Y	see above	4,6,7, 9-11, 13-15, 18-30, 37-43, 45-48

X	US,A,5 358 941 (BECHARD SIMON R ET AL) 25 October 1994 see column 4 - column 5; examples 1-3 see column 4, line 15	1-3,5, 8-10, 12-17, 21, 31-36, 44,49
Y	see above	4,6,7, 11, 18-20, 22-30, 37-43, 45-48

X	EP,A,0 298 666 (AMERICAN HOME PROD) 11 January 1989 see page 2, line 1 - line 8 see page 3 - page 9; examples 1-7	1-3,5, 16-18, 31,44,49
Y	see above	4,6-11, 13-15, 19-30, 33,35, 37-43, 45-48

Y	WO,A,94 22435 (ORION YHTYMAE OY ;HALONEN MATTI AUKUSTI (FI); LEINONEN ULLA INKERI) 13 October 1994 see the whole document	22,26, 27,39,40

Y	EP,A,0 519 820 (ADIR) 23 December 1992 see the whole document	25,30,43

Y	WO,A,93 23025 (ALZA CORP) 25 November 1993 see the whole document	24,29,42

Y	DE,A,39 41 703 (SANOL ARZNEI SCHWARZ GMBH) 20 June 1991 see the whole document	23,28,41

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. .tional Application No
PCT/IE 95/00062

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9208463	29-05-92	FR-A-	2669221	22-05-92
		AT-T-	111734	15-10-94
		CA-A-	2094122	16-05-92
		DE-D-	69104220	27-10-94
		DE-T-	69104220	26-01-95
		EP-A-	0557389	01-09-93
		ES-T-	2060417	16-11-94
		JP-T-	6502420	17-03-94
EP-A-0511767	04-11-92	AU-B-	1522992	05-11-92
		CA-A-	2067307	30-10-92
		CN-A-	1066184	18-11-92
		CZ-A-	9302270	16-03-94
		JP-A-	6157309	03-06-94
		NO-A-	933806	22-10-93
		NZ-A-	242486	23-12-93
		SK-A-	117793	11-05-94
		WO-A-	9219228	12-11-92
US-A-5358941	25-10-94	AU-B-	5611594	22-06-94
		CN-A-	1098907	22-02-95
		CZ-A-	9501346	18-10-95
		EP-A-	0690719	10-01-96
		FI-A-	952685	01-06-95
		NO-A-	952184	01-06-95
		PL-A-	309245	02-10-95
		WO-A-	9412200	09-06-94
		ZA-A-	9308979	03-08-94
EP-A-0298666	11-01-89	DE-A-	3883098	16-09-93
		DE-T-	3883098	02-12-93
		ES-T-	2058288	01-11-94
		IE-B-	61676	30-11-94
		US-A-	4904477	27-02-90
WO-A-9422435	13-10-94	AU-B-	4023695	15-02-96
		AU-B-	663995	26-10-95
		AU-B-	6430094	24-10-94
		CA-A-	2137164	13-10-94
		EP-A-	0643578	22-03-95

5739

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. .onal Application No
PCT/IE 95/00062

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9422435		FI-A-	945716	02-12-94
		JP-T-	7506845	27-07-95
		NO-A-	944631	01-12-94
		NZ-A-	263568	26-01-96
EP-A-0519820	23-12-92	FR-A-	2677886	24-12-92
		AT-T-	131050	15-12-95
		AU-B-	651894	04-08-94
		AU-B-	1834392	24-12-92
		CA-A-	2071408	19-12-92
		DE-D-	69206495	18-01-96
		JP-A-	5186346	27-07-93
		US-A-	5334392	02-08-94
		ZA-A-	9204482	18-08-93
WO-A-9323025	25-11-93	AU-B-	666735	22-02-96
		AU-B-	4247393	13-12-93
		CA-A-	2132865	25-11-93
		FI-A-	945311	11-11-94
		NO-A-	944249	14-11-94
		US-A-	5411740	02-05-95
		ZA-A-	9303349	15-06-94
DE-A-3941703	20-06-91	NONE		